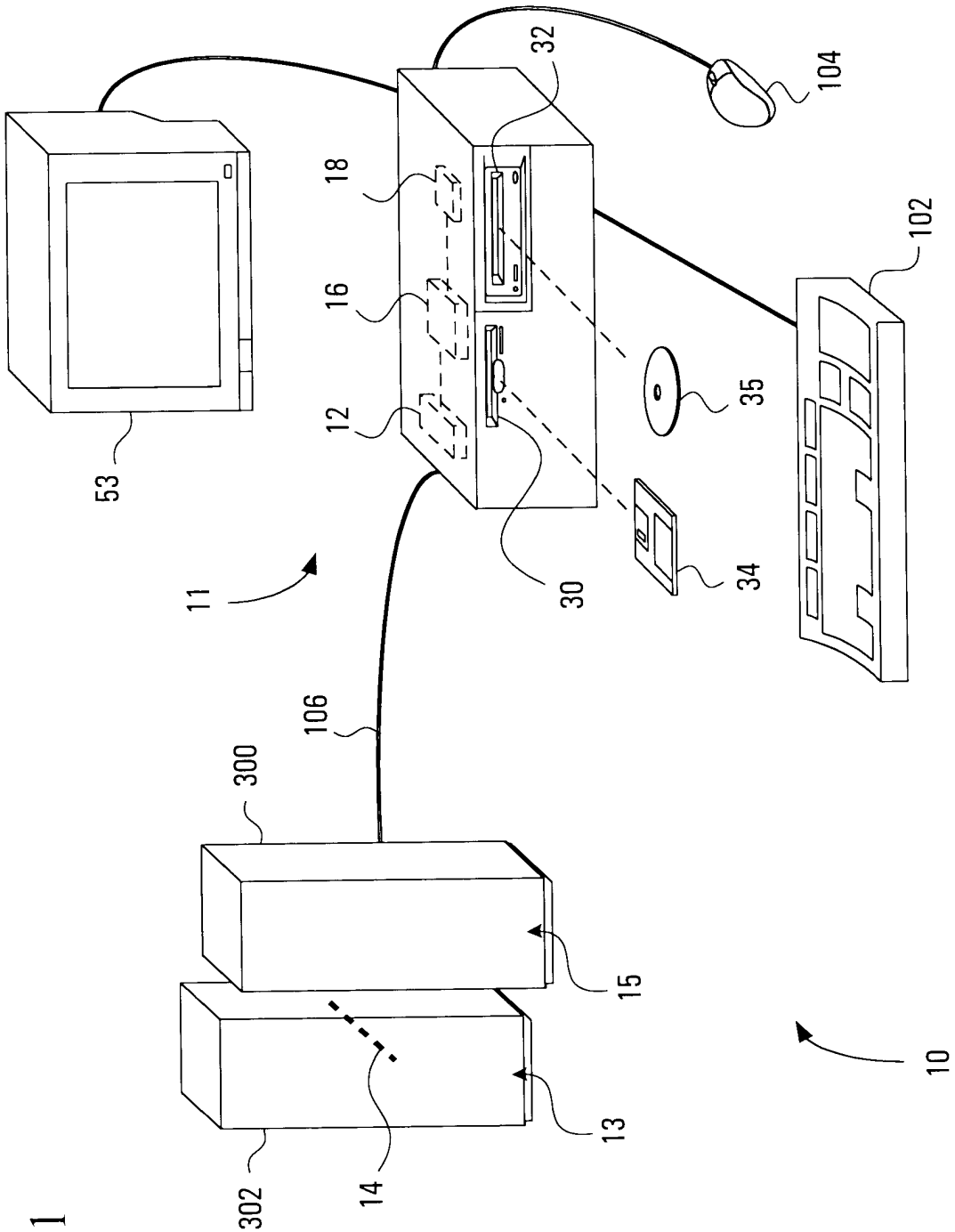


FIG. 1

APR 1 0 2003

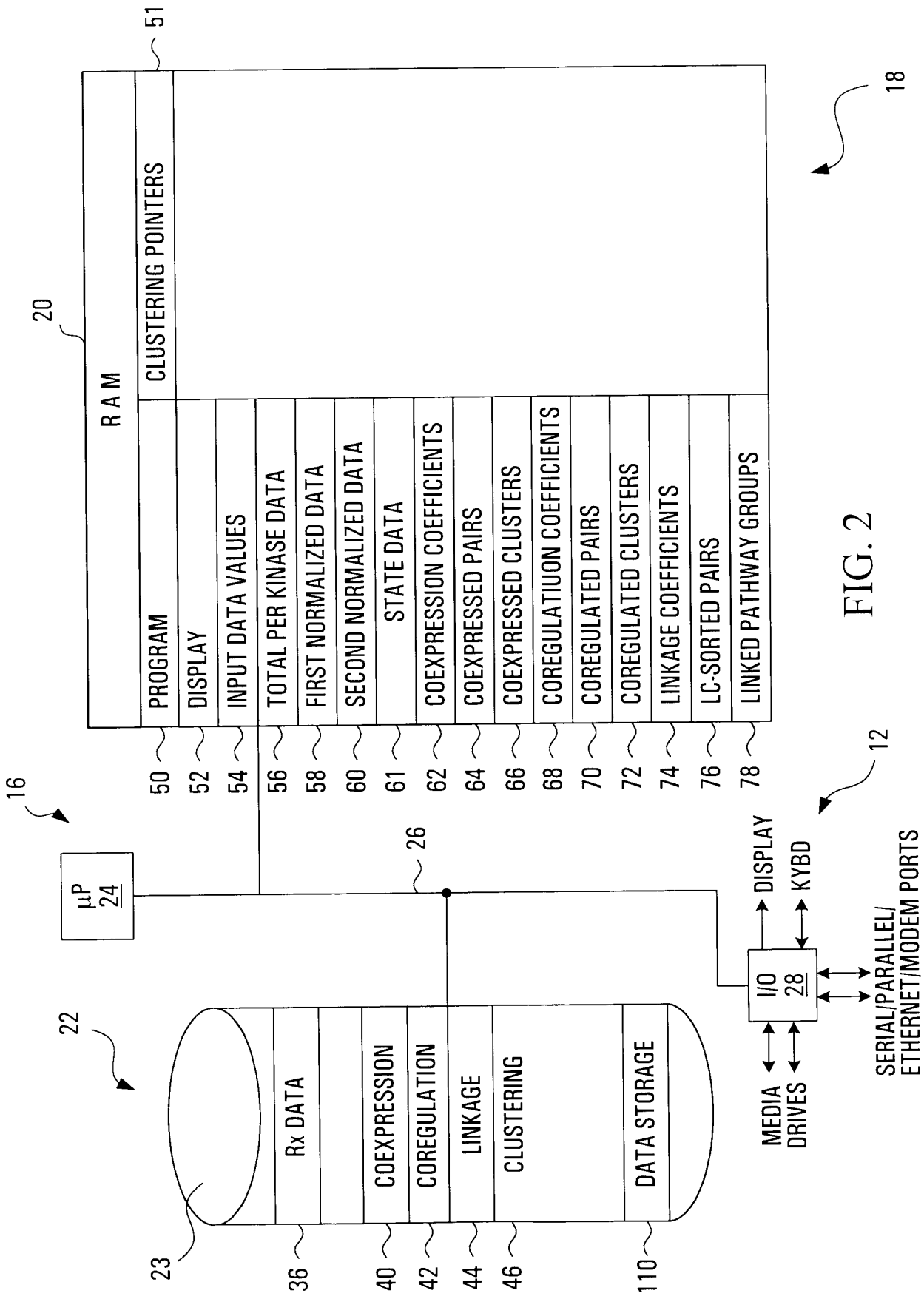


FIG. 2

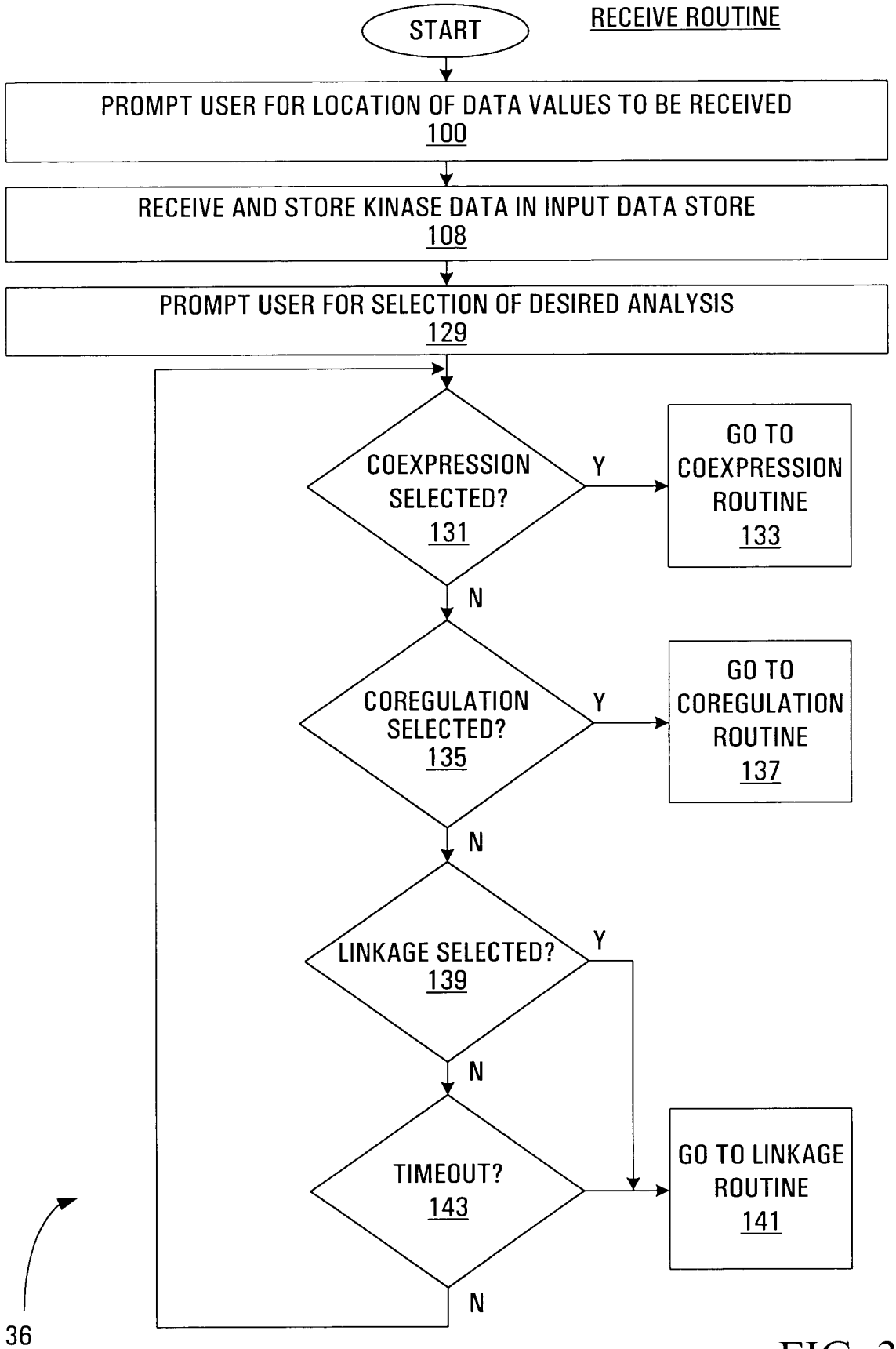
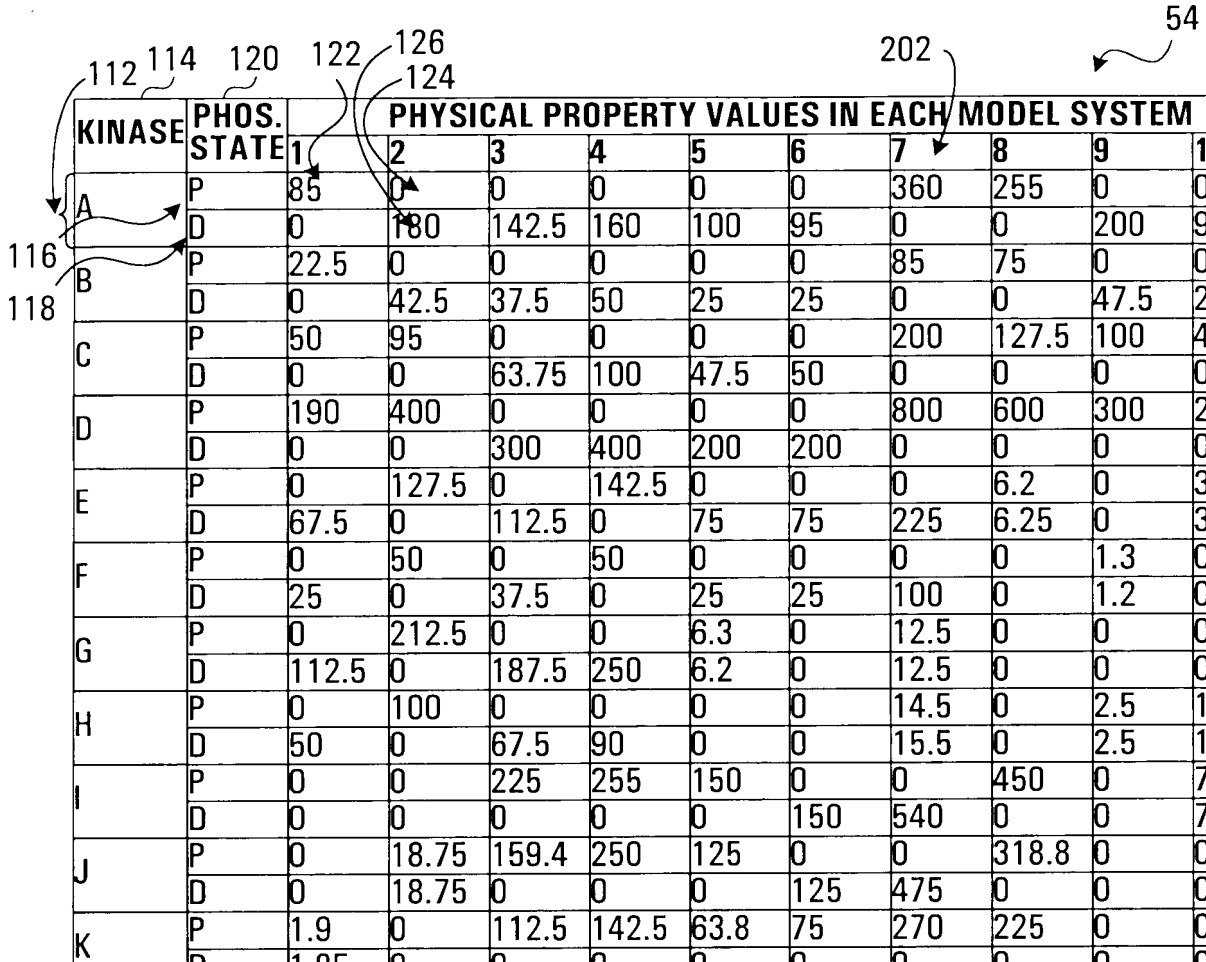

RECEIVE ROUTINE
START
PROMPT USER FOR LOCATION OF DATA VALUES TO BE RECEIVED
100
RECEIVE AND STORE KINASE DATA IN INPUT DATA STORE
108
PROMPT USER FOR SELECTION OF DESIRED ANALYSIS
129
COEXPRESSION SELECTED?
131
Y
GO TO COEXPRESSION ROUTINE
133
N
COREGULATION SELECTED?
135
Y
GO TO COREGULATION ROUTINE
137
N
LINKAGE SELECTED?
139
Y
N
TIMEOUT?
143
GO TO LINKAGE ROUTINE
141
N
36

FIG. 3



KINASE	PHOS. STATE	PHYSICAL PROPERTY VALUES IN EACH MODEL SYSTEM									
		1	2	3	4	5	6	7	8	9	10
A	P	85	0	0	0	0	0	360	255	0	0
	D	0	180	142.5	160	100	95	0	0	200	90
B	P	22.5	0	0	0	0	0	85	75	0	0
	D	0	42.5	37.5	50	25	25	0	0	47.5	25
C	P	50	95	0	0	0	0	200	127.5	100	42.5
	D	0	0	63.75	100	47.5	50	0	0	0	0
D	P	190	400	0	0	0	0	800	600	300	200
	D	0	0	300	400	200	200	0	0	0	0
E	P	0	127.5	0	142.5	0	0	0	6.2	0	3.75
	D	67.5	0	112.5	0	75	75	225	6.25	0	3.75
F	P	0	50	0	50	0	0	0	0	1.3	0
	D	25	0	37.5	0	25	25	100	0	1.2	0
G	P	0	212.5	0	0	6.3	0	12.5	0	0	0
	D	112.5	0	187.5	250	6.2	0	12.5	0	0	0
H	P	0	100	0	0	0	0	14.5	0	2.5	1.2
	D	50	0	67.5	90	0	0	15.5	0	2.5	1.3
I	P	0	0	225	255	150	0	0	450	0	7.5
	D	0	0	0	0	0	150	540	0	0	7.5
J	P	0	18.75	159.4	250	125	0	0	318.8	0	0
	D	0	18.75	0	0	0	125	475	0	0	0
K	P	1.9	0	112.5	142.5	63.8	75	270	225	0	0
	D	1.85	0	0	0	0	0	0	0	0	0
L	P	0	0	75	100	45	50	200	142.5	2.6	2.4
	D	0	0	0	0	0	0	0	0	2.4	2.6
M	P	0	0	0	0	100	85	400	0	10	0
	D	0	0	0	0	0	0	0	300	10	0
N	P	2.5	2.5	0	0	25	25	100	0	0	0
	D	2.5	2.5	0	0	0	0	0	75	0	0
O	P	0	0	4.7	6.25	106.3	125	475	0	19	6.4
	D	0	0	4.7	6.25	0	0	0	318.75	18.5	6.1
P	P	0	0	0	0	150	142.5	600	0	0	0
	D	0	0	0	0	0	0	0	450	0	0
Q	P	0	0	5.625	0	0	0	0	8	100	42.5
	D	50	85	5.6	0	0	0	0	7	0	0
R	P	0	0	0	5	0	5	15	0	190	100
	D	100	200	0	5	0	5	15	0	0	0
S	P	0	0	0.95	0	1.2	0	0	0	42.5	22.5
	D	21.25	50	0.95	0	1.3	0	0	0	0	0
T	P	0	0	0	0	0	0	15	0	250	118.75
	D	125	225	0	0	0	0	15	0	0	0
Erk1	P	0	0	0	0	0	0	0	0	0	0
	D	50	100	75	100	50	50	200	150	100	50

FIG. 4

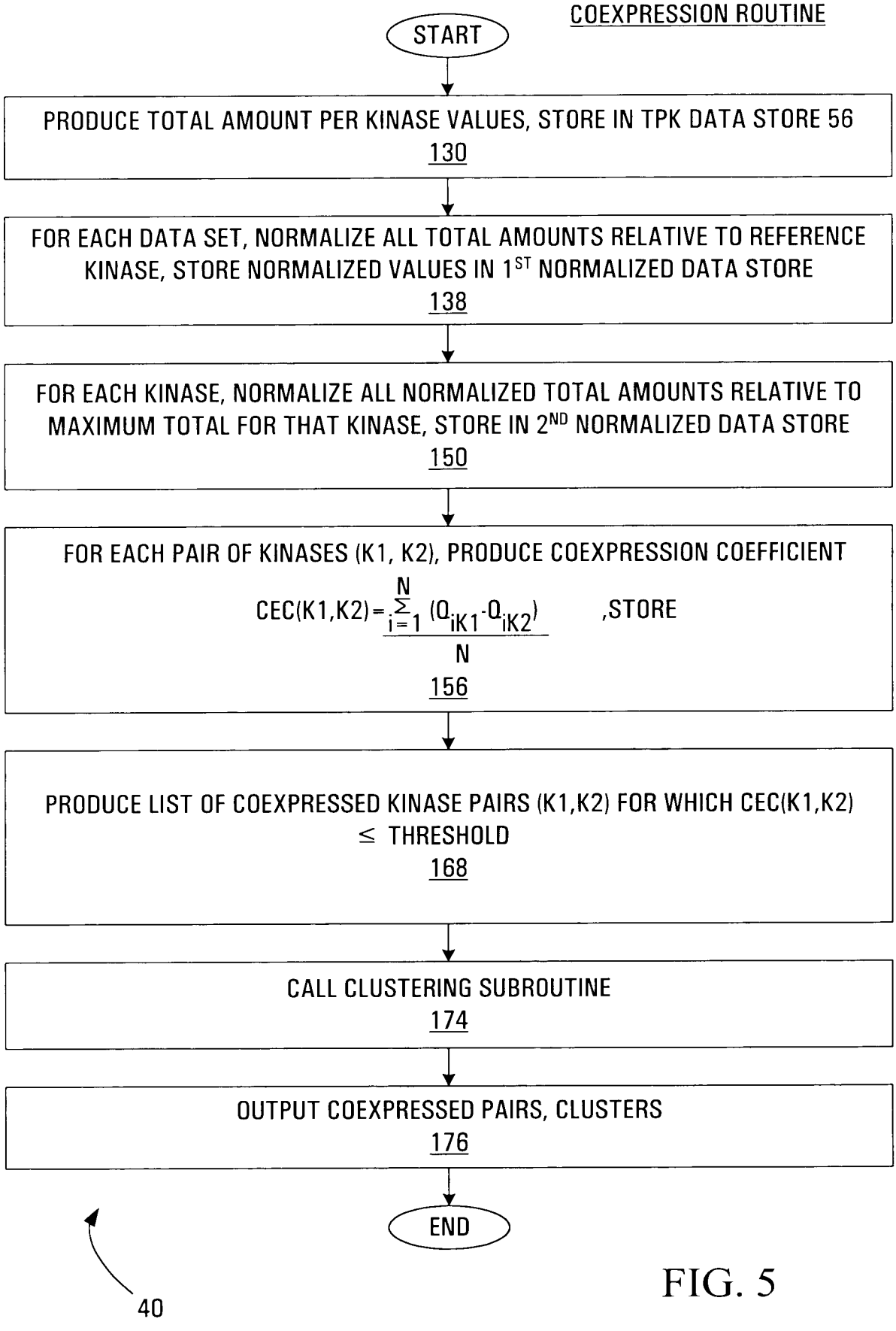

COEXPRESSION ROUTINE
START
PRODUCE TOTAL AMOUNT PER KINASE VALUES, STORE IN TPK DATA STORE 56
130
FOR EACH DATA SET, NORMALIZE ALL TOTAL AMOUNTS RELATIVE TO REFERENCE KINASE, STORE NORMALIZED VALUES IN 1ST NORMALIZED DATA STORE
138
FOR EACH KINASE, NORMALIZE ALL NORMALIZED TOTAL AMOUNTS RELATIVE TO MAXIMUM TOTAL FOR THAT KINASE, STORE IN 2ND NORMALIZED DATA STORE
150
FOR EACH PAIR OF KINASES (K1, K2), PRODUCE COEXPRESSION COEFFICIENT
CEC(K1,K2) = Σ(i=1 to N) (Q_iK1 - Q_iK2) / N ,STORE
156
PRODUCE LIST OF COEXPRESSED KINASE PAIRS (K1,K2) FOR WHICH CEC(K1,K2) ≤ THRESHOLD
168
CALL CLUSTERING SUBROUTINE
174
OUTPUT COEXPRESSED PAIRS, CLUSTERS
176
END
40

FIG. 5

TOTAL PER PROTEIN (TPP) DATA STORE

SYSTEM KINASE	1	2	3	4	5	6	7	8	9	10
A	85	180	142.5	160	100	95	360	255	200	90
B	22.5	42.5	37.5	50	25	25	85	75	47.5	25
C	50	95	63.75	100	47.5	50	200	127.5	100	42.5
D	190	400	300	400	200	200	800	600	300	200
E	67.5	127.5	112.5	142.5	75	75	255	11.25	0	7.5
F	25	50	37.5	50	25	25	100	0	2.5	0
G	112.5	212.5	187.5	250	12.5	0	25	0	0	0
H	50	100	67.5	90	0	0	30	0	5	2.5
I	0	0	225	255	150	150	540	450	0	15
J	0	37.5	159.4	250	125	125	475	318.8	0	0
K	3.75	0	112.5	142.5	63.8	75	270	225	0	0
L	0	0	75	100	45	50	200	142.5	5	5
M	0	0	0	0	100	85	400	300	20	0
N	5	5	0	0	25	25	100	75	0	0
O	0	0	9.4	12.5	106.3	125	475	318.75	37.5	12.5
P	0	0	0	0	150	142.5	600	450	0	0
Q	50	85	11.25	0	0	0	0	15	100	42.5
R	100	200	0	10	0	10	30	0	190	100
S	21.25	50	1.9	0	2.5	0	0	0	42.5	22.5
T	125	225	0	0	0	0	30	0	250	118.75
Erk 1	50	100	75	100	50	50	200	150	100	50

134, 140, 136, 56, 132, 144, 142

FIG. 6

146 FIRST NORMALIZED DATA STORE

151

SYSTEM KINASE	1	2	3	4	5	6	7	8	9	10	MAX VALUE
A	170	180	190	160	200	190	180	170	200	180	200
B	45	42.5	50	50	50	50	42.5	50	47.5	50	50
C	100	95	85	100	95	100	100	85	100	85	100
D	380	400	400	400	400	400	400	400	300	400	400
E	135	127.5	150	142.5	150	150	127.5	7.5	0	15	150
F	50	50	50	50	50	50	50	0	2.5	0	50
G	225	212.5	250	250	25	0	12.5	0	0	0	250
H	100	100	90	90	0	0	15	0	5	5	100
I	0	0	300	255	300	300	270	300	0	30	300
J	0	37.5	212.5	250	250	250	237.5	212.5	0	0	250
K	7.5	0	150	142.5	127.5	150	135	150	0	0	150
L	0	0	100	100	90	100	100	95	5	10	100
M	0	0	0	0	200	170	200	200	20	0	200
N	10	5	0	0	50	50	50	50	0	0	50
O	0	0	12.5	12.5	212.5	250	237.5	212.5	37.5	25	250
P	0	0	0	0	300	285	300	300	0	0	300
Q	100	85	15	0	0	0	0	10	100	85	100
R	200	200	0	10	0	20	15	0	190	200	200
S	42.5	50	2.5	0	5	0	0	0	42.5	45	50
T	250	225	0	0	0	0	15	0	250	237.5	250

148

58

FIG. 7

152 SECOND NORMALIZED DATA STORE

SYSTEM KINASE	1	2	3	4	5	6	7	8	9	10
A	85	90	95	80	100	95	90	85	100	90
B	90	85	100	100	100	100	85	100	95	100
C	100	95	85	100	95	100	100	85	100	85
D	95	100	100	100	100	100	100	100	75	100
E	90	85	100	95	100	100	85	5	0	10
F	100	100	100	100	100	100	100	0	5	0
G	90	85	100	100	10	0	5	0	0	0
H	100	100	90	90	0	0	15	0	5	5
I	0	0	100	85	100	100	90	100	0	10
J	0	15	85	100	100	100	95	85	0	0
K	5	0	100	95	85	100	90	100	0	0
L	0	0	100	100	90	100	100	95	5	10
M	0	0	0	0	100	85	100	100	10	0
N	10	5	0	0	100	100	100	100	0	0
O	0	0	5	5	85	100	95	85	15	10
P	0	0	0	0	100	95	100	100	0	0
Q	100	85	15	0	0	0	0	10	100	85
R	100	100	0	5	0	10	7.5	0	95	100
S	85	100	5	0	10	0	0	0	85	90
T	100	90	0	0	0	0	6	0	100	95

154 — rows A–L

158 — rows M–O

60

160 — row T

FIG. 8

COEXPRESSION COEFFICENTS STORE

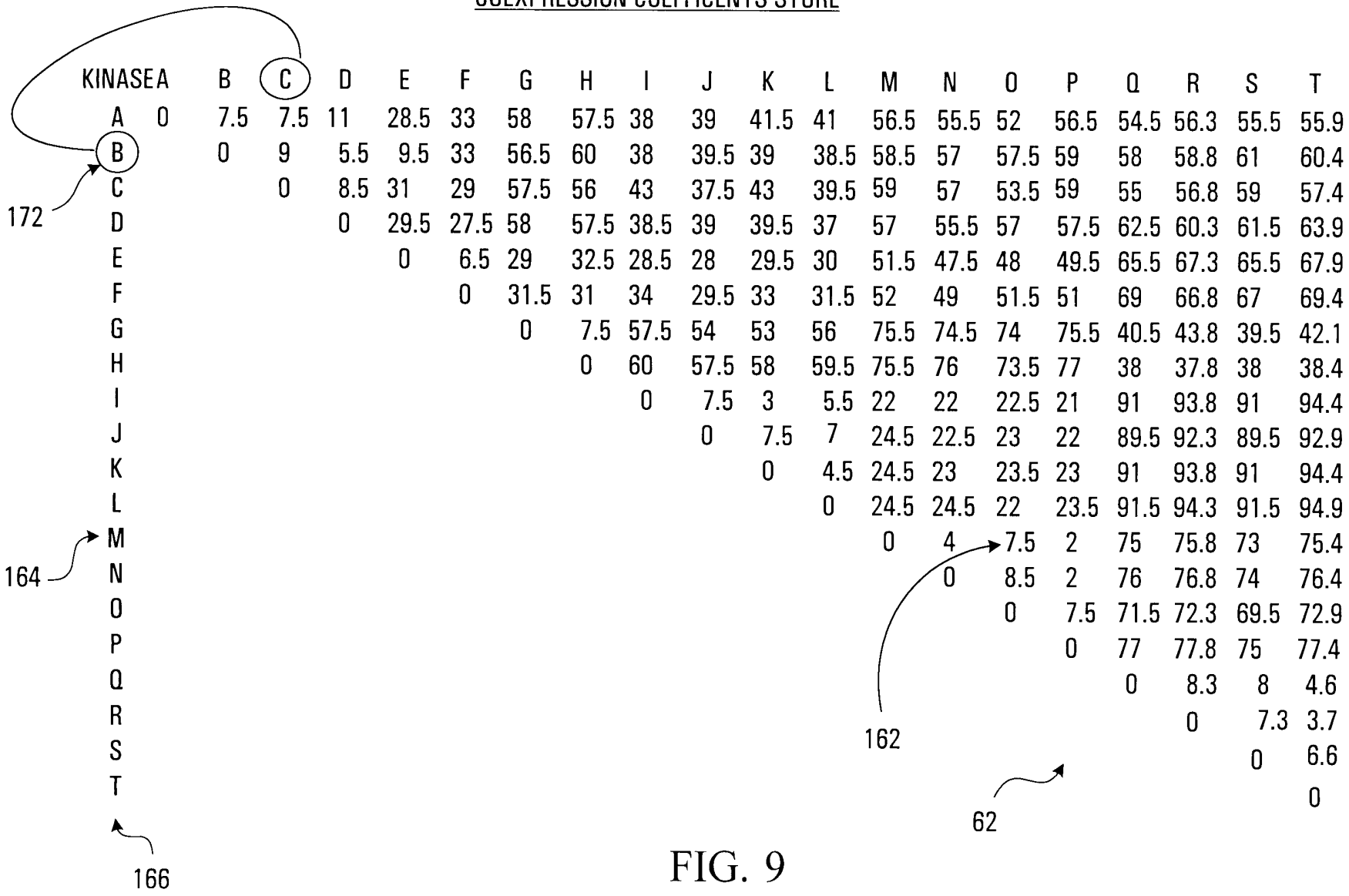


FIG. 9

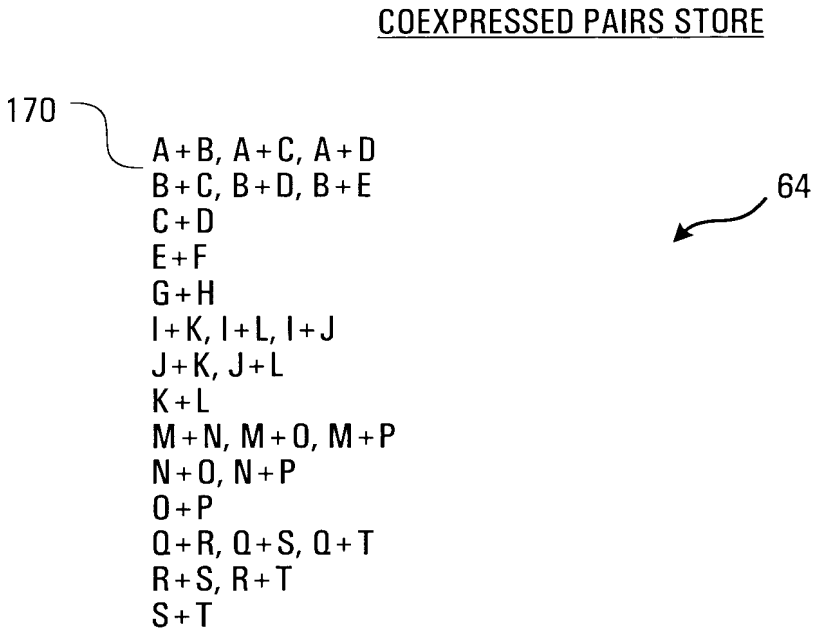

COEXPRESSED PAIRS STORE
170
A+B, A+C, A+D
B+C, B+D, B+E
C+D
E+F
G+H
I+K, I+L, I+J
J+K, J+L
K+L
M+N, M+O, M+P
N+O, N+P
O+P
Q+R, Q+S, Q+T
R+S, R+T
S+T
64

FIG. 10

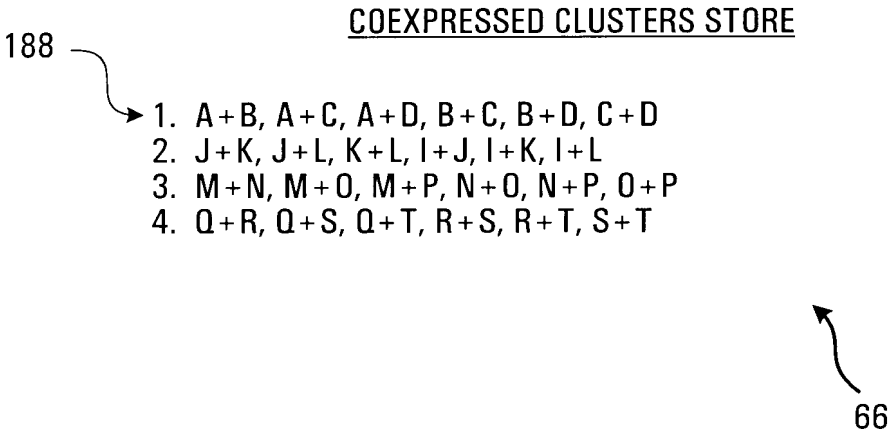

COEXPRESSED CLUSTERS STORE
188
1. A+B, A+C, A+D, B+C, B+D, C+D
2. J+K, J+L, K+L, I+J, I+K, I+L
3. M+N, M+O, M+P, N+O, N+P, O+P
4. Q+R, Q+S, Q+T, R+S, R+T, S+T
66

FIG. 11

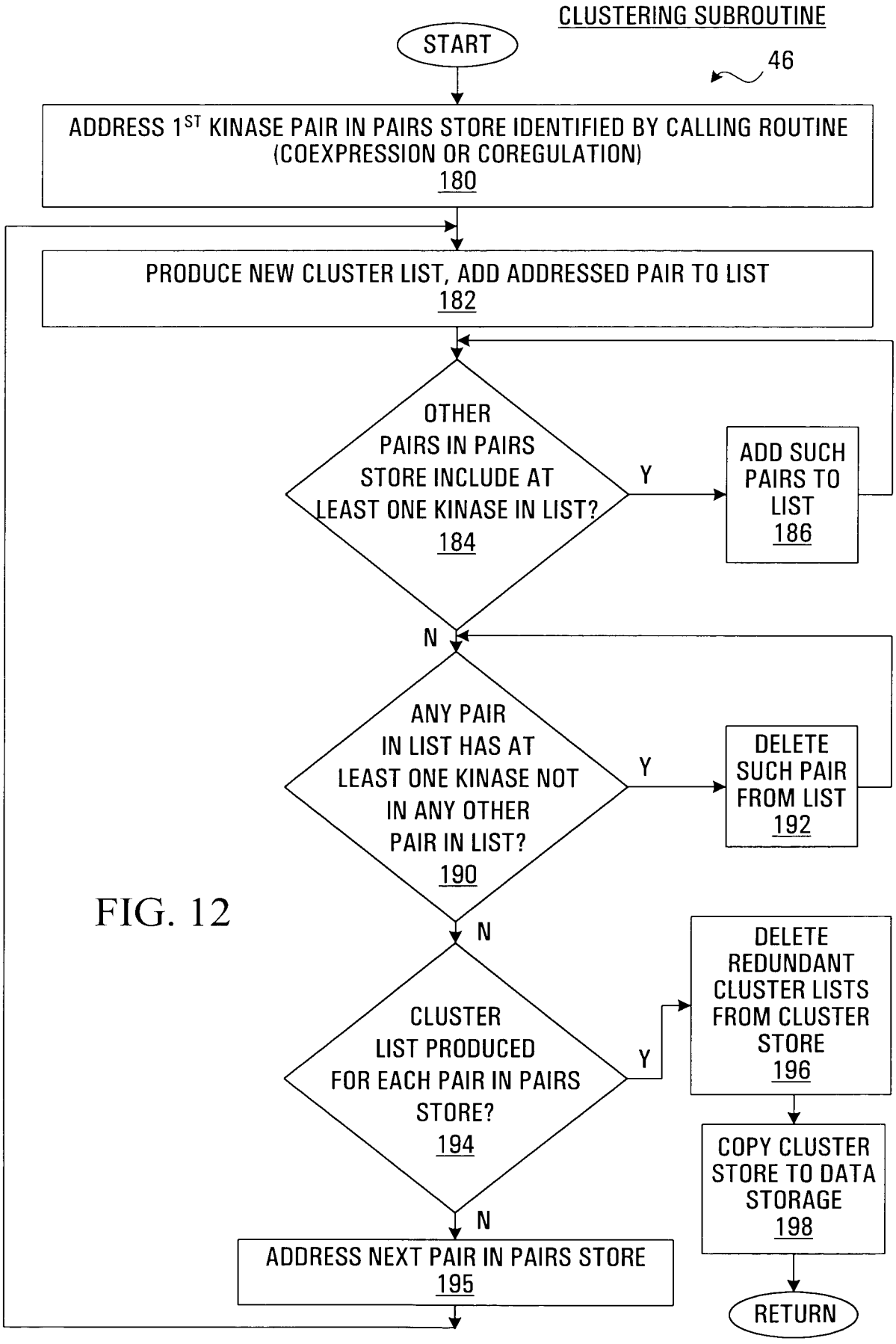

CLUSTERING SUBROUTINE
START
46
ADDRESS 1ST KINASE PAIR IN PAIRS STORE IDENTIFIED BY CALLING ROUTINE (COEXPRESSION OR COREGULATION)
180
PRODUCE NEW CLUSTER LIST, ADD ADDRESSED PAIR TO LIST
182
OTHER PAIRS IN PAIRS STORE INCLUDE AT LEAST ONE KINASE IN LIST?
184
Y
ADD SUCH PAIRS TO LIST
186
N
ANY PAIR IN LIST HAS AT LEAST ONE KINASE NOT IN ANY OTHER PAIR IN LIST?
190
Y
DELETE SUCH PAIR FROM LIST
192
N
CLUSTER LIST PRODUCED FOR EACH PAIR IN PAIRS STORE?
194
Y
DELETE REDUNDANT CLUSTER LISTS FROM CLUSTER STORE
196
COPY CLUSTER STORE TO DATA STORAGE
198
N
ADDRESS NEXT PAIR IN PAIRS STORE
195
RETURN

FIG. 12

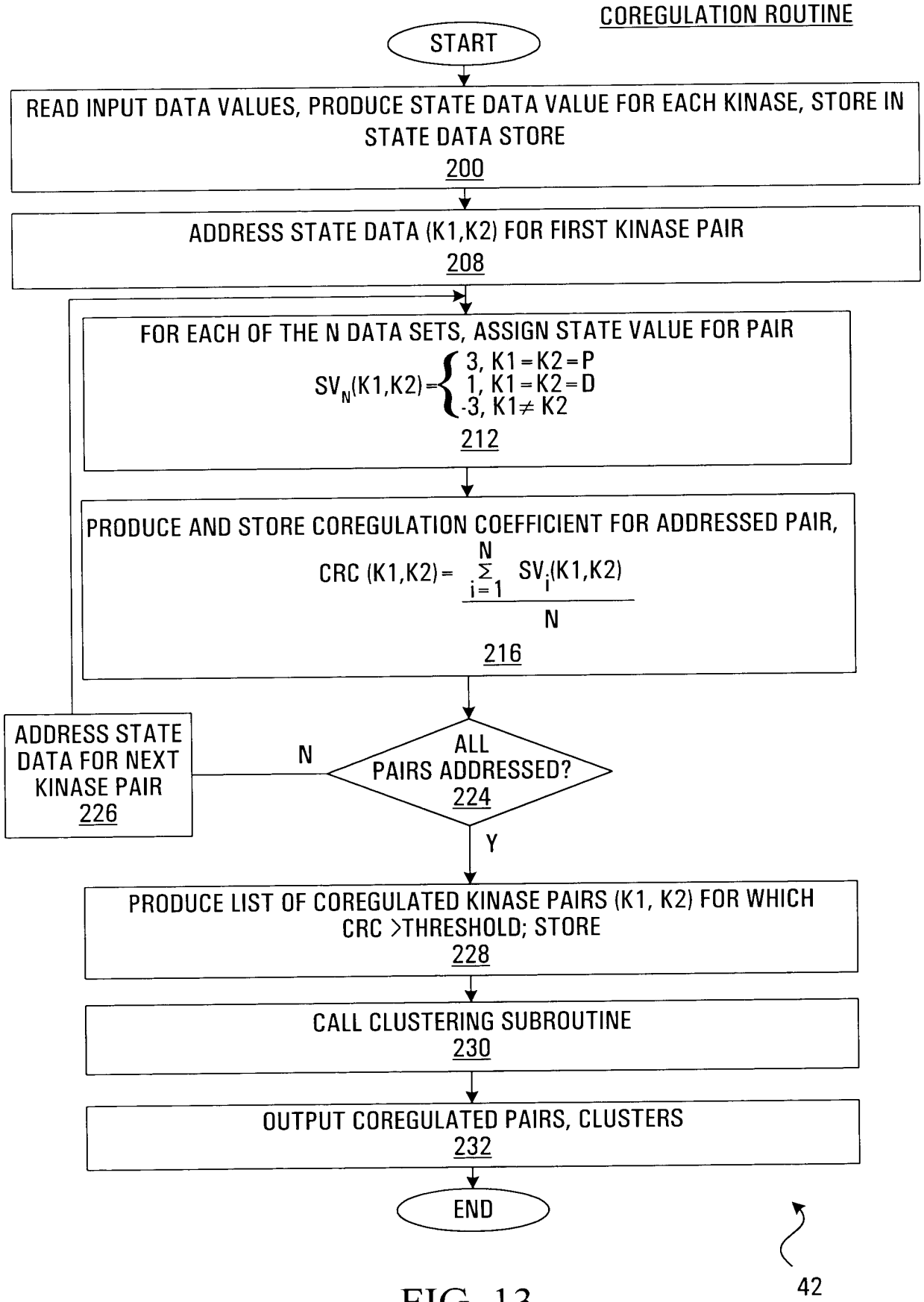

COREGULATION ROUTINE
START
READ INPUT DATA VALUES, PRODUCE STATE DATA VALUE FOR EACH KINASE, STORE IN STATE DATA STORE
200
ADDRESS STATE DATA (K1,K2) FOR FIRST KINASE PAIR
208
FOR EACH OF THE N DATA SETS, ASSIGN STATE VALUE FOR PAIR
$SV_N(K1,K2) = \begin{cases} 3, K1=K2=P \\ 1, K1=K2=D \\ -3, K1 \neq K2 \end{cases}$
212
PRODUCE AND STORE COREGULATION COEFFICIENT FOR ADDRESSED PAIR,
$CRC(K1,K2) = \frac{\sum_{i=1}^{N} SV_i(K1,K2)}{N}$
216
ADDRESS STATE DATA FOR NEXT KINASE PAIR
226
N
ALL PAIRS ADDRESSED?
224
Y
PRODUCE LIST OF COREGULATED KINASE PAIRS (K1, K2) FOR WHICH CRC >THRESHOLD; STORE
228
CALL CLUSTERING SUBROUTINE
230
OUTPUT COREGULATED PAIRS, CLUSTERS
232
END
42

FIG. 13

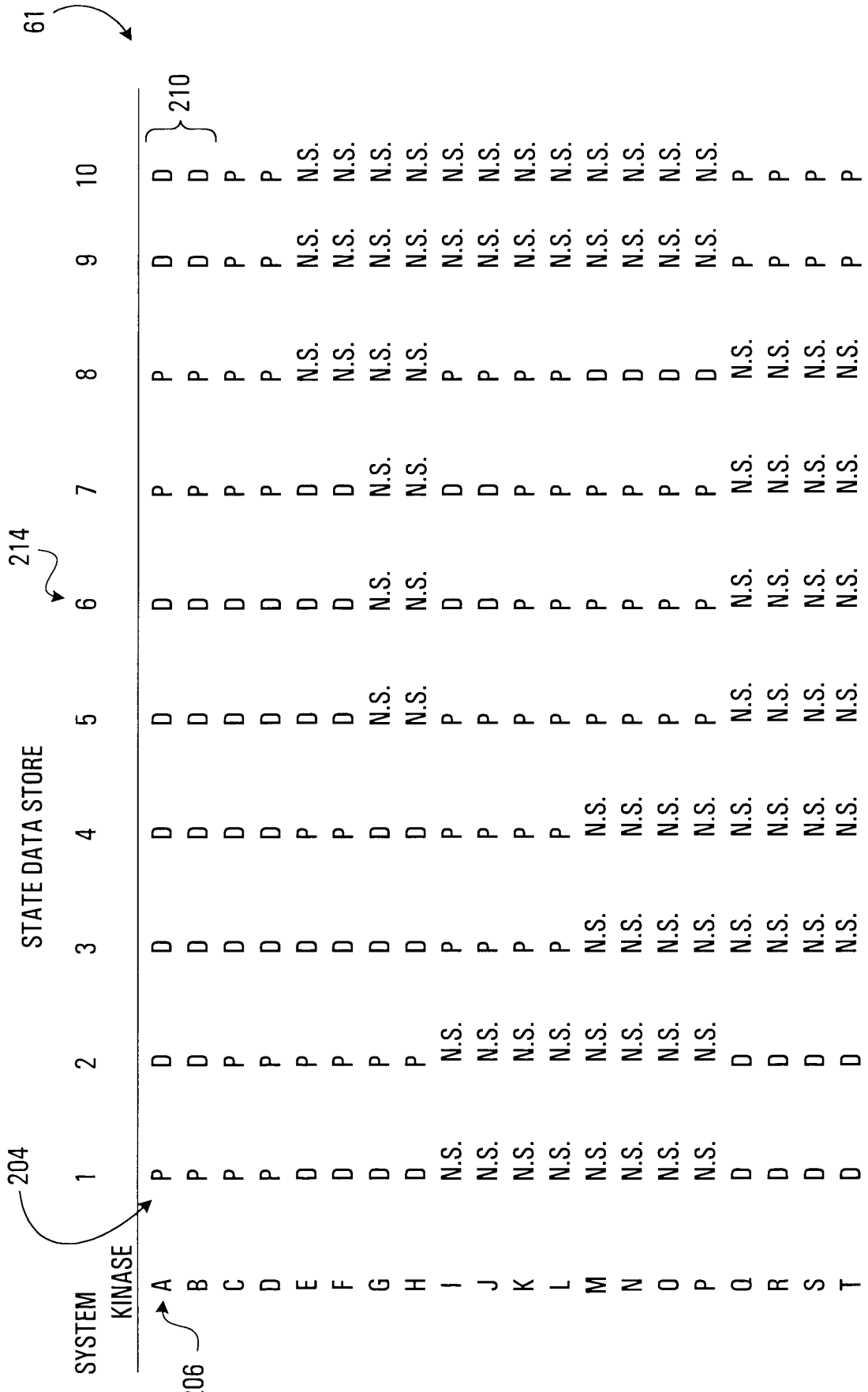

61
204
214
210
206
SYSTEM KINASE
STATE DATA STORE
1 2 3 4 5 6 7 8 9 10
A P D D D D P P D D
B P D D D D P P D D
C P P D D D P P P P
D P P D D D P P P P
E D P D P D D D N.S. N.S. N.S.
F D P D P D D N.S. N.S. N.S.
G D P D D N.S. N.S. N.S. N.S. N.S.
H D P D D N.S. N.S. N.S. N.S. N.S.
I N.S. N.S. P P P D P N.S. N.S. P
J N.S. N.S. P P P D P N.S. N.S. P
K N.S. N.S. P P P P P N.S. N.S. P
L N.S. N.S. P P P P P N.S. N.S. P
M N.S. N.S. N.S. N.S. P P D N.S. N.S. P
N N.S. N.S. N.S. N.S. P P D N.S. N.S. P
O N.S. N.S. N.S. N.S. P P D N.S. N.S. P
P N.S. N.S. N.S. N.S. P P D N.S. N.S. P
Q D D N.S. N.S. N.S. N.S. N.S. P P P
R D D N.S. N.S. N.S. N.S. N.S. P P P
S D D N.S. N.S. N.S. N.S. N.S. P P P
T D D N.S. N.S. N.S. N.S. N.S. P P P

FIG. 14

COREGULATION COEFFICIENTS STORE

KINASE	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	1.60	0.40	0.40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B		0	0.40	0.40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C			0	2.20	0	0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
D				0	0	0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
E					0	1.570	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
F						0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
G							0	1.50	0	0	0	0	0	0	0	0	0	0	0	0
H								0	0	0	0	0	0	0	0	0	0	0	0	0
I									0	2.330	1.00	1.00	0	0	0	0	0	0	0	0
J										0	1.00	1.00	0	0	0	0	0	0	0	0
K											0	3.00	1.50	1.50	1.50	1.50	0	0	0	0
L												0	1.50	1.50	1.50	1.50	0	0	0	0
M													0	2.50	2.50	2.50	0	0	0	0
N														0	2.50	2.50	0	0	0	0
O															0	2.50	0	0	0	0
P																0	0	0	0	0
Q																	0	2.00	2.00	2.00
R																		0	2.00	2.00
S																			0	2.00
T																				0

220

218

68

222

FIG. 15

COREGULATED PAIRS

A+B, A+C, A+D
B+C, B+D
C+D, C+G, C+H
D+G, D+H
E+F, E+G, E+H
F+G, F+H
G+H
I+J, I+K, I+L
J+K, J+L
K+L, K+M, K+N, K+O, K+P
L+M, L+N, L+O, L+P
M+N, M+O, M+P
N+O, N+P
O+P
Q+R, Q+S, Q+T
R+S, R+T
S+T

70

FIG. 16

COREGULATED CLUSTERS

1. A+B, A+C, A+D, B+C, B+D, C+D, C+G, C+H, D+G, D+H, E+F, E+G, E+H, F+G, F+H, G+H
2. I+J, I+K, I+L, J+K, J+L, K+L, K+M, K+N, K+O, K+P, M+N, M+O, M+P, N+O, N+P, O+P
3. Q+R, Q+S, Q+T, R+S, R+T, S+T

72

FIG. 17

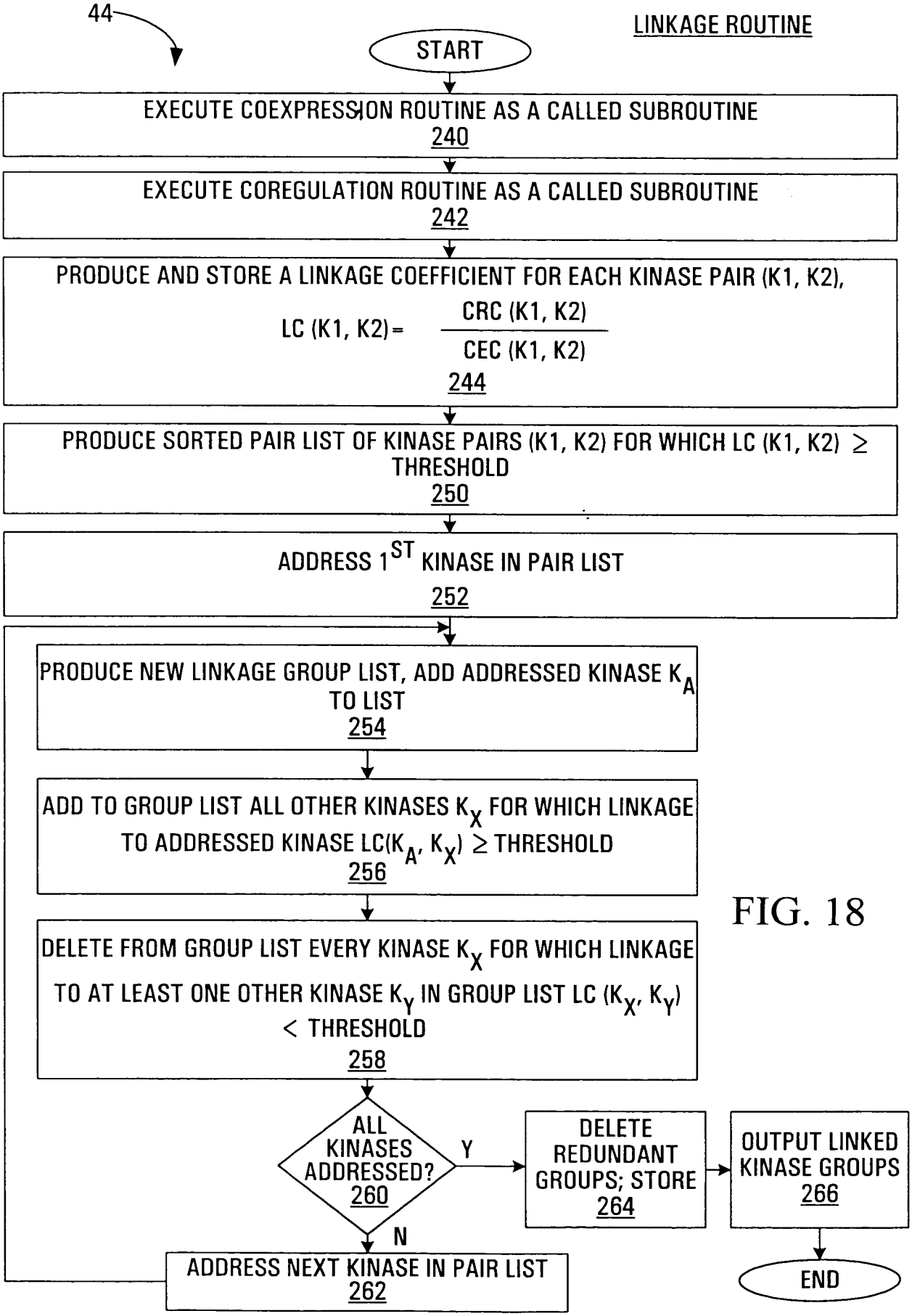

44
LINKAGE ROUTINE
START
EXECUTE COEXPRESSION ROUTINE AS A CALLED SUBROUTINE
240
EXECUTE COREGULATION ROUTINE AS A CALLED SUBROUTINE
242
PRODUCE AND STORE A LINKAGE COEFFICIENT FOR EACH KINASE PAIR (K1, K2),
LC (K1, K2) = CRC (K1, K2) / CEC (K1, K2)
244
PRODUCE SORTED PAIR LIST OF KINASE PAIRS (K1, K2) FOR WHICH LC (K1, K2) ≥ THRESHOLD
250
ADDRESS 1ST KINASE IN PAIR LIST
252
PRODUCE NEW LINKAGE GROUP LIST, ADD ADDRESSED KINASE K_A TO LIST
254
ADD TO GROUP LIST ALL OTHER KINASES K_X FOR WHICH LINKAGE TO ADDRESSED KINASE LC(K_A, K_X) ≥ THRESHOLD
256
DELETE FROM GROUP LIST EVERY KINASE K_X FOR WHICH LINKAGE TO AT LEAST ONE OTHER KINASE K_Y IN GROUP LIST LC (K_X, K_Y) < THRESHOLD
258
ALL KINASES ADDRESSED?
260
Y
N
DELETE REDUNDANT GROUPS; STORE
264
OUTPUT LINKED KINASE GROUPS
266
END
ADDRESS NEXT KINASE IN PAIR LIST
262

FIG. 18

LINKAGE COEFFICIENTS STORE

KINASE	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	21.3	5.3	3.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B		0	4.4	7.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C			0	25.9	0	0	0.9	0.9	0	0	0	0	0	0	0	0	0	0	0	0
D				0	0	0	0.9	0.9	0	0	0	0	0	0	0	0	0	0	0	0
E					0	24.2	1.7	1.5	0	0	0	0	0	0	0	0	0	0	0	0
F						0	1.6	1.6	0	0	0	0	0	0	0	0	0	0	0	0
G							0	20	0	0	0	0	0	0	0	0	0	0	0	0
H								0	0	0	0	0	0	0	0	0	0	0	0	0
I									0	31.1	33.3	18.2	0	0	0	0	0	0	0	0
J										0	13.3	14.3	0	0	0	0	0	0	0	0
K											0	66.7	6.1	6.5	6.4	6.5	0	0	0	0
L												0	6.1	6.1	6.8	6.4	0	0	0	0
M													0	62.5	33.3	125	0	0	0	0
N														0	29.4	125	0	0	0	0
O															0	33.3	0	0	0	0
P																0	0	0	0	0
Q																	0	24.1	25	43.5
R																		0	27.4	54.1
S																			0	30.3
T																				0

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FIG. 19

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PAIR NUMBER	LINKAGE COEFFICIENT	KINASE PAIR
1	125	M, P
2	125	N, P
3	66.7	K, L
4	62.5	M, N
5	54.1	R, T
6	43.5	Q, T
7	33.3	I, K
8	33.3	M, O
9	33.3	O, P
10	31.1	I, J
11	30.3	S, T
12	29.4	N, O
13	27.4	R, S
14	25.9	C, D
15	25	Q, S
16	24.2	E, F
17	24.1	Q, R
18	21.3	A, B
19	20	G, H
20	18.2	I, L
21	14.3	J, L
22	13.3	J, K
23	7.3	B, D
24	6.8	L, O
25	6.5	K, N
26	6.5	K, P
27	6.4	K, O
28	6.4	L, P
29	6.1	K, M
30	6.1	L, M
31	6.1	L, N
32	5.3	A, C
33	4.4	B, C
34	3.6	A, D
35	1.7	E, G
36	1.6	F, G
37	1.6	F, H
38	1.5	E, H
39	0.9	C, G
40	0.9	C, H
41	0.9	D, G
42	0.9	D, H

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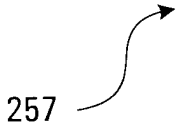
FIG. 20



1. A, B, C, D
2. C, D, G, H
3. E, F, G, H
4. I, J, K, L
5. K, L, M, N, O, P
6. Q, R, S, T

FIG. 21